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(54) Title: COMPOUNDS USEFUL AGAINST DISEASES OF THE COLON AND METHODS FOR ORALLY ADMINISTERING SAME

(57) Abstract

This invention is an enteric-coated granular formulation capable of targeting or persisting in the colonic region and a method for using the formulation to treat disorders of the colon wall.

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TITLE: COMPOUNDS USEFUL AGAINST DISEASES OF THE COLON AND METHODS FOR ORALLY ADMINISTERING SAME

BACKGROUND OF THE INVENTION

This application claims priority to U.S. Provisional Patent Application No. 60/033,235, filed on December 5, 1996.

1. Field of the Invention

This invention is an enteric coated capsule including a therapeutic agent and methods for using the enteric coated capsule for treating diseases and disorders of the lower digestive system and particularly for treating diseases associated with the surface of the colon such as colon cancer.

2. The Prior Art

With 56,000 deaths and 149,000 new cases diagnosed in 1994, carcinoma of the colon and rectum is the fourth most common cancer in the United States. Unfortunately, colon cancers are considered to be innately resistant to a variety of chemotherapeutic agents used alone or in combination. The most effective current treatment is by complete surgical excision of the affected area but follow-up shows that there is only a 58% survival rate five years after surgery. There is an urgent need to improve early detection of the disease and to provide more effective post-operative treatment. Patients are currently treated with a combination of chemotherapy, radiotherapy and immunotherapy. Systemic chemotherapy with 5-flourouracil (5-FU), alone or in combination with other chemotherapeutic agents, is effective but side effects due to drug interactions at sites

other than those associated with the tumors often result in low patient compliance and higher failure rates. From a drug delivery perspective it would be preferable to deliver smaller quantities of the antineoplastic directly to the tumor site, thereby improving the prospects for a successful treatment outcome.

Methods for drug delivery to the colon have recently been discussed (Friend, 1992; Mrsny, 1992). However, there is still no method or composition available that can deliver small quantities of antineoplastics directly to the colorectal wall where most tumors are to be found.

SUMMARY OF THE INVENTION

The present invention is directed to the enteric coated pellets comprising a mucoadhesive material and a therapeutic agent that are able to deliver the therapeutic agent to the mammalian colorectal wall.

Further, this invention is a method for treating colon cancer in a mammal with few toxic side-effects due in part to the ability to administer lower dosages of a therapeutic agent and due in part to the ability to target the colon with the anti-cancer therapeutic agent.

In one embodiment, this invention is an oral pharmaceutical dosage form. The dosage form comprises a plurality of particles, each particle further comprises at least one therapeutic agent that is active against disorders of the mammalian colon, and at least one mucoadhesive. Each particle is coated with an enteric coating.

In another embodiment, this invention is an oral pharmaceutical dosage form. The oral dosage form comprises a plurality of particles. Each particle further comprises from about 15 to about 25 wt% 5-fluorouracil, and from about 75 to about 85 wt% hydroxyproplymethylcellulose. Each particle is coated with from about 1 to about 5 wt% of an enteric coating of at least one acrylic acid copolymer that swells in an aqueous environment having a pH of from about 6.8 to about 7.2 or greater.

In still another embodiment, this invention is a method for for treating disorders of the mammalian colon wall by orally administering pharmaceutical dosage forms of this invention to a mammal suffering from a colorectal disease, and specifically to a mammal with colon cancer.

DESCRIPTION OF THE PREFERRED EMBODIMENT

This invention is an enteric-coated formulation useful for the oral treatment of disorders and diseases of the mammalian colon and methods for using the oral pharmaceutical formulation to treat diseases of the mammalian colon. The composition of this invention comprises at least one therapeutic agent combined with a mucoadhesive material to form small particles. The particles are thereafter coated with one or more enteric coatings that swell and degrade when exposed to the pH found in the colon. When the enteric coating has swelled or degraded, the therapeutic agent and mucoadhesive are exposed. The mucoadhesive attaches to mucous on the colon surface and the therapeutic agent then targets colon wall diseases. The enteric coated compositions have pH-solubility profiles which initially protect drug-containing HPMC granules from water or enzymic attack until the pH of the GI luminal contents approximates that of the colon.

The enteric coated formulations of this invention include at least one therapeutic agent that targets a disease of the colorectal wall. It is preferred that the therapeutic chosen agent targets tumor cells projecting into or associated with the colorectal wall. Such therapeutic materials are commonly referred to as antineoplastic agents. Useful antineoplastic agents include alkylating agents, including alklysulfonates, aziridines, epoxides, nitrogen mustards, and nitrosureas, and antibiotics such as bleomycin and andreomycin. A highly preferred antineoplastic agent is 5-fluorouracil. 5-fluorouracil has been shown to be an effective chemotherapeutic agent against colon cancer.

The therapeutic agents should be present in the particles of this invention in an amount sufficient to effectively treat the targeted colorectal wall diseases. The preferred

composition should contain from about 5 to about 50 wt % 5-fluorouracil and most preferably from about 15 to about 25 wt % of 5-fluorouracil.

The composition of this invention also includes a mucoadhesive. The mucoadhesive is combined with the therapeutic agent into particles. The mucoadhesive facilitates the delivery of the therapeutic material to diseases of the colorectal wall by adhering to mucus membranes associated with the colorectal wall. Any known mucoadhesive compounds may be used in the composition of this invention. It is preferred that the mucoadhesive composition used is a form of hydroxycellulose and preferably hydroxypropylmethylcellulose or hydroxymethylcellulose. The mucoadhesive should be present in the particles incorporated into the composition of this invention in amount ranging from about 50 to about 95 wt % and preferably from about 80 to about 95 wt %.

The mucoadhesive and therapeutic agents are combined by standard granulation methods to give particles comprising at least one therapeutic agent and at least one mucoadhesive. The size of the particles should range from about 10 to 200 microns and preferably from about 50 to about 150 microns. Once formed, the particles are coated with an enteric coating that swells and degrades to expose mucoadhesive at a pH of from about 6.8 to about 7.2. The pH target is the general pH of the lower GI tract in the vicinity of the colon. It is preferred that the enteric coating is an acrylic acid copolymer. Preferred acrylic acid copolymers are manufactured by Röhm under the trade name EUDRAGIT. The compositions of this invention may include one or more enteric coating agents. It is preferred that the enteric coating is present in the composition of this invention in amount ranging from about 0.1 to about 10 wt %.

The enteric coating is typically applied to the therapeutic agent/mucoadhesive particles using standard fluidized bed or spray coating techniques. The enteric coating composition is typically supplied pre-dissolved in a solvent solution. The particles are coated with the solution, the solvent solution is allowed to volatilize from the coated particles, and a solid enteric coating remains on each particle.

The enteric coated particles are intended to be administered to a mammal orally. This can be achieved by placing the particles into a tablet, into a gelatin capsule, into a dispersion, or in any other vehicle known in the art for providing an orally consumable therapeutic agent. Once ingested, the enteric coating protects the therapeutic agent and mucoadhesive containing particles from attack and digestion at the pH conditions in the mammalian stomach and upper intestinal tract. As the particles pass through the GI tract, the pH slowly increases from a value of about 5.0 in the stomach to a pH value of from about 6.8 to about 7.2 or higher, in the mammalian colon, at which pH the enteric coating swells and the mucoadhesive containing particle is exposed. Once exposed the mucoadhesive adheres to mucus membranes on the colorectal wall an therapeutic agent is delivered to disease sites associated with the colorectal wall with very little absorption of the therapeutic agent into the mammalian body. In the situations where cancer of the colon is being treated, the mucus layer covering cancerous cells is typically very thin and the therapeutic agent is delivered quickly and effectively essentially only to the diseased portions of the colorectal wall.

The compounds of the present invention are useful for treating diseases and disorders of the mammalian colon and specifically cancer and pre-cancer diseases in the human colon. The compounds of this invention are administered to mammals orally. The

compositions of this invention may be administered in suitable oral pharmaceutical dosage forms. The term pharmaceutical dosage form refers to items such as tablets, capsules, liquids and powders, comprising compositions of this invention alone or in the presence of one or more pharmaceutical excipients. Those skilled in the pharmaceutical arts will recognize a wide variety of excipients useful in oral therapeutic dosage forms.

The oral pharmaceutical dosage forms of this invention may include one or more additives in the form of pharmaceutically acceptable additives. Useful additives include solvents, solubilizers, preservatives, thickeners, wetting agents, colorants, resorption accelerators, antioxidants, light stabilizers, tackifiers, viscosity increasing substances, fillers, flavorings, lubricating agents, and any other pharmaceutical composition additive known to those skilled in the art.

In the pharmaceutical dosage forms described herein, the active compounds can be present in the form of a mixture with at least one other active compound. Alternatively, or in addition, the pharmaceutical dosage forms of the invention can, in addition to at least one compound active against diseases and disorders of the colon, include any pharmaceutical compound that is capable of treating any known malady or disorder where the administration of both together create no unacceptable adverse effects.

Methods for treating diseases and disorders of the colon by the oral administration of an effective quantity of the chosen compound or combinations thereof in a solid oral pharmaceutical dosage form. Ready-to-use oral pharmaceutical dosage forms of this invention contain the active compound in concentrations of from 10 ppm to 20 per cent by weight, and preferably of from 0.1 to 10 per cent by weight. In general, it has proved advantageous to administer amounts of approximately 0.01mg to approximately 100 mg of active compound per kg of body weight per day to achieve effective results.

The amount and frequency of administration of oral pharmaceutical dosage forms of this invention will be readily determined by one skilled in the art depending upon, among other factors, the effectiveness of delivery of the active compound, and the age and condition of the patient. Oral pharmaceutical dosage forms may be administered one to ten times daily for acute or chronic disease.

The oral pharmaceutical dosage forms of this invention are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms.

EXAMPLES

The following materials were used in the Examples of embodiments of this invention: 5-Fluorouracil (5-FU), Iodouracil (IU), barium sulfate and polyvinyl alcohol were obtained from Sigma Chemical Co. (St. Louis, MO). Acrylic acid copolymers, Eudragit®-S100, L100, hydroxypropylmethylcellulose (HPMC), Methocel® K4M and K100M were kindly supplied by Röhm (Malden, MA) and Dow Chemical (Midland, MI), respectively. A physical blend, L/S of Eudragit S-100 and L-100 (1:1), prepared in this laboratory, was also evaluated. Ethyl acetate, methanol, HPLC-grade water and methylene chloride were purchased from Fisher Chemical Co. (Fair Lawn, NJ), as were other reagent grade chemicals and buffers. Ultrasphere XL ODS, Ultrasphere C18 and Sep-pak C18 HPLC columns were obtained from Alltech Associates (Deerfield, IL).

Female Sprague-Dawley rats weighing approximately 200-250g were obtained from Sasco-King Animal Laboratories (Sasco, Inc., Omaha, NE). The animals were maintained on a standard laboratory diet with water *ad libitum* at the Biological Resources Laboratories, University of Illinois of Chicago, in accordance with protocols approved by the University Animal Care Committee.

EXAMPLE 1

Preparation of Core Granules

5-FU at 20% w/w and HPMC 'Methocel'® K4M or 'Methocel'® K100M were mixed in a glass mortar and pestle and the powders massed with 70% (v/v) ethanol before granulating and drying in an air over overnight at 40°C. The dried granules were sieved through a 200 mesh stainless steel sieve to remove fines. Barium sulfate granules were prepared by a similar technique, mixing the 'Methocel'® K100M with an equal

weight of the barium sulfate.

Preparation of Enteric Coated Microspheres.

Enteric coated microspheres were prepared by an oil-in-water solvent evaporation technique adopted from the procedures of Beck et al., (1979) and Ciftci et al, (1994). The HPMC granules (350 mg) with 5-FU or barium sulfate, were suspended in a 7% w/v solution of the selected acrylic acid copolymer in methylene chloride. The polymer/granule suspension was added to 750 mL aqueous polyvinyl alcohol, (PVA) 0.35% w/v, at 37°C. Agitation was maintained at 500 rpm using a glass stirrer overnight to allow evaporation of the methylene chloride. The microspheres were collected by filtration, washed with distilled water, dried in air under ambient room conditions and stored in a desiccator at 4°C prior to use. The particle size of the microspheres was kept between 425 μm - 500 μm for all experiments by collecting the fraction between numbers 40 and 35 standard sieves.

Light microscopy (Olympus-CH2) and scanning electron microscopy (Jeol-JSM-35C, Tokoyo, Japan) evaluation confirmed the spherical appearance of the coated microspheres containing 5-FU, with no crystal material visible on the surface.

Weighed amounts of the microspheres were extracted in methanol at ambient room temperatures for 24 hours, followed by analysis for 5-FU content by UV-spectroscopy (Beckman-DV-65 Spectrophotometer) at 266 nm by reference to a calibration curve of 5-FU in methanol.

Eudragit-S100, L100 and L/S microspheres prepared by using the modified solvent evaporation method were spherical and smooth. All core particles were individually and completely coated with Eudragit polymers. No evidence of crystalline

material could be seen on the surface of the coated microspheres for microspheres in which the core particles had a drug loading of 20% w/w.

The Eudragit, 5-FU and HPMC concentrations in the dispersion phase were kept constant for all formulations. The microsphere yield was found to be better than 80% with all polymers. The drug loading was below 90% of nominal when preparing, and coating, low or high molecular weight HPMC granules (Table 1). However, the use of the higher molecular weight HPMC 'Methocel® K100M' resulted in a statistically significant increase in the incorporation of 5-FU (Table 1). This may be due to an increased exclusion of the aqueous PVA solution during the dispersion process (Beck et al.,1979; Citfci et al., 1994).

EXAMPLE 2

Release Studies

5-FU release from the microspheres was measured using the dialysis sac method at 37± 0.1°C, shaking at 50 cycles/minute. Measurements were made by a fixed pH procedure using USP XXII buffers to cover the range pH 1.5-7.8. In addition, in order to stimulate the variable pH conditions experienced by an orally administered product, as it transits down the GI tract, a variable pH method was used. Here the system started with stimulated gastric fluid (USP XXII) (without enzymes) as the dissolution medium, to which was added, at one hourly interval over 8 hours, and then at 12 hourly intervals up to 48 hours, a volume equal to the withdrawn sample volume of 0.5 M dibasic potassium phosphate and 2 M sodium hydroxide mixture solution. Experimentally, the pH varied from 1.5-7.8 over a period of 48 hours. The release medium pH was measured for each sample which were also assayed for 5-FU content by UV-spectrophotometry at 266 nm as described.

Dissolution studies demonstrated that the 'Eudragit'-L and the blend of 'Eudragit'-L and -S released drug at pH 5.8 whereas the granules coated with 'Eudragit'-S alone did not release drug until the pH had reached pH 6.8. This was confirmed by both fixed and variable pH methods. Comparison of the various molecular weight grades of core 'Methocels' suggested that only the 'Eudragit'-S coated 'Methocel' K100M retarded the 5-FU release enough to be feasible. This may be attributed to the combination of a number of factors, including the relative hydrophobicity of the coating and the increased viscosity of the dissolving HPMC core.

EXAMPLE 3

In Vivo GI Transit of Barium Sulfate Microspheres

For the determination of the GI transit time, barium sulfate microspheres or a barium sulfate dispersion, (5% w/v) in 1.5 mL water were administered by oral gavage to each of eighteen rats fasted overnight. The animals were fasted for the duration of studies but allowed access to water throughout. The rats were lightly anaesthetized with Innovar-Vet® (Pitman Moore, Mundelein, IL) for the oral gavage procedure. The GI transit time was evaluated by x-ray examination (Universal, Unimatic 325, Chicago, IL). Anaesthetized animals were examined by stretching over an x-ray film canister by means of light bandage pressure. Exposures of 300 milliampere for 1/120 seconds at 2 hourly intervals were sufficient to demonstrate the position of the barium sulfate as it moved down the gut. Preliminary experiments demonstrated a slower rate of movement of the formulation down the bowel once it had reached the colorectal region. The animals were examined over a period of 27 hours.

Using the rat as a model, it was evident that the normal transit time along with the entire gut of a fasted animal was below 8 hours, Table 1, below.

TABLE 1

time (h)	site of free barium sulfate (as a suspension)	site of barium sulfate loaded microspheres
0-2	stomach and small intestine	stomach
2-4	small intestine and cecum	small intestine and cecum
4-6	colon	ascending colon

6-8	eliminated from body	ascending and transverse colon
8-12	----	descending colon
12-24	----	descending colon and rectum

The microspheres containing barium sulfate or the barium sulfate suspension had removed to the cecum within 2 hours and cecum and small intestine transit times of both suspension and microsphere formulations were remarkably constant (Table 2). Similar results have been obtained for GI transit times in humans (Harris et al., 1989).

X-ray photographs of enteric-coated HPMC particles containing 50% barium sulfate confirmed that transit down to the colonic region was at least as rapid as that of the otherwise unformulated barium sulfate suspension. Indeed, this system persisted in the colon for some 27 hours after administration (Table 2). This may be explained by formulation factors such as viscosity, swelling properties and bioadhesion of the exposed core. The subsequent movement of the barium sulfate marker may be due to the intrinsic movement of the interstitial layer of mucous lining of the colorectal region to which the delivery system is adhering. In addition, the process of gastric emptying in the fasted state is governed by the interdigestive myoelectric complex (IMC), a cyclical pattern of contractile activity (Gruber et al., 1987). The cycle of the IMC was broken with a bolus of 100-150 mL water in the dog (Gupat et al., 1988). In our study, the dose may have been too small and drinking small volumes of water ad libitum may not have been sufficient to break the IMC.

EXAMPLE 4

Administration of Formulations containing 5-FU

Female Sprague-Dawley rats (~ 200g) were used in this experiment. Animals were fasted for 18 hours prior to and during the study but allowed access to water throughout. Animals were divided into four individual groups. Four groups of six animals (Groups 1 through IV) received oral dosage forms of 5-FU under light anesthesia using 2 mg/kg ketamine intraperitoneally. Group I (control) received a suspension of uncoated HPMC (Methocel K100M) granules with 5-FU (15 mg/ kg) in sterile water (1.5 mL) and Groups II, III and IV received a suspension of Eudragit-S coated microspheres containing 5-FU in water (1.5 mL) by oral gavage. Each group of animals was allowed to recover and sacrificed by carbon dioxide asphyxiation at 6 hours for the control (Group I) and at 8h, 12h, 24h for Groups II and IV, respectively after dosing.

The carcass was opened by bilateral thoracotomy as rapidly as possible following death. Each animal was placed on an ice pack and blood (10 mL) immediately obtained by intracardiac puncture for collection in heparinized tubes. Blood samples were centrifuged (Sorvall RC-5B Refrigerated Superspeed Centrifuge) at 2000 x g for 10 minutes and serum separated as quickly as possible. The GI tract was removed and the mesenteric and fatty acid tissues separated. The GI tract was segmented into the stomach, small intestine, cecum and colon. The luminal contents were removed by applying gentle pressure with wet scissors to the tissues. Organs and luminal contents were weighed. The organs were cut open longitudinally and rinsed with saline solution (0.9% NaCl) to remove any remaining luminal contents. The remaining GI tract tissues were cut into small pieces, diluted with HPLC-grade water and homogenized at 4°C with

a Termolyne-Vortex (Type 16700) mixer. After centrifugation of tissue homogenates (1000 x g/10 min/4°C), the fatty layer was discarded and supernatants were used for HPLC analysis. Luminal contents were diluted to 7.5% with HPLC-grade water and the suspended contents vortex homogenized (at 4°C), followed by centrifugation as above. The resulting supernatants were refrigerated prior to HPLC analysis.

The HPLC method was based on that of Barberi-Heyob, et al (1992). The chromatographic system consisted of a Water Assoc. Model-600 solvent delivery system with a Water Assoc. Model-490 UV-VIS absorbance detector. The columns used were a Ultrasphere XL ODS, 3 μm (75 mm x 4.6 mm ID) and Ultrasphere C18 (45 mm x 4.6 mm ID) (Altech Associates, Deerfield, IL). The mobile phase was water-methanol (95:5, v/v) pumped at a flow rate of 1 mL/min at 25°C. The mobile phase was out-gassed under vacuum before use. The detection wavelength was 266 nm.

Blood Sample Pretreatment. To glass tubes were added 600 μL of the aqueous plasma samples with 0.5 μg/mL iodouracil (IU) as an internal standard and separated on a dry Sep-pak C18 column for 5 min. Two 2 mL volumes of ethyl acetate-methanol (95:5, v/v) were used to extract the 5-FU from the aqueous layer. The extract (4 mL) was collected in a glass tube and concentrated by evaporation in a stream of dry air at 37°C for 15 minutes. To the sample was added 500 μL HPLC-grade water, heated at 37°C for 10 minutes, vortex-mixed and filtered. Samples of 25 μL were injected into the HPLC column, as described.

Tissue Homogenate Pretreatment: The aqueous homogenates (1 mL), with 0.5 μg/mL iodouracil (IU) as an internal standard, were added to glass tubes. The samples were added to the dry Sep-pak C18 column for 5 minutes, as described.

Standard Calibration Curve Preparation: Blank plasma and GI segment homogenates samples were spiked in duplicate with 10 μL/mL of the 5-FU standard solution in water at concentrations ranging from 0.01 - 0.5 μg/mL and subjected to the sample preparation procedure described above. Calibration curves were constructed by plotting the ratio of the peak used of 5-FU to that of internal standard versus 5-FU concentrations. The best fit straight line was determined by using a Microsoft-Excel computer program.

Results were presented as means ± standard deviations (SD). Statistical comparisons were made with analysis of variance (ANOVA) using the Microsoft-Excel computer program.

Analysis of the 5-FU content of various tissues six hours after administration of the uncoated formulation, that is, at a time beyond which the gastrointestinal tract would ordinarily be anticipated to have substantially emptied, demonstrated large quantities of the drug in both blood and stomach, Table 2. This is likely to be due to continued adhesion of the HPMC particles to the wall of the stomach after administration, with subsequent absorption into the blood stream at that point. Accumulation of 5-FU in the upper region of the GI tract after oral administration is consistent with the fact that the permeability coefficient of 5-FU in upper regions was significantly higher than that of the colon and rectum due to a balance between water-solubility and lipophilicity.

TABLE 2

TISSUES	UNCOATED GRANULES[a]	EUDRAGIT-S COATED MICROSPHERES[b]		
	6Hours (n = 6)	8Hours (n = 6)	12Hours (n = 6)	24Hours (n = 6)
Blood (μg.mL)	64.3 ± 3.7	2.2 ± 0.2	3.1 ± 1.0	4.2 ± 0.01
Stomach (μg/g)	1000.5 ± 509.0	< 0.01	< 0.01	< 0.01
Small Intestine (μg/g)	140.2 ± 15.1	< 0.01	0.1 ± 0.0	0.3 ± 0.0
Cecum (μg/g)	358 ± 71.5	< 0.01	0.1 ± 0.0	0.5 ± 0.1
Colon Homogenates (μg/g)	413 ± 40.08	40.8 ± 3.5	829.4 ± 134.9	628.9 ± 191.0
Colon Content (μg/g)	90.9 ± 12.7	103.8 ± 17.8	406.4 ± 78.4	374.0 ± 206.6

a: HPMC (Methocel K100M) granules with 5-FU (uncoated)

b: Eudragit - S - coated microspheres containing HPMC (Methocel K100M) granules with 5-FU

Analysis of tissues from animals give enteric coated microspheres showed little drug (under the detection limit) in any tissues except the colon between 8 hours, well after the measured GI transit time under the previous experimental conditions, and 24 hours, Table 3, above. The amounts of drug in the colonic contents increased between the 8 and 12 hour samples and were still significant ($p < 0.01$) at the 24 hour time point, Table 2.

The composition of this invention enable a drug to be selectively delivered to a tissue and not, as has been the emphasis in previous investigations, through the tissue. The delivery, in small quantities, of an antineoplastic drug such as 5-FU to the inner surface of the colon may be effective in destroying small tumors that arise spontaneously in this region. An oral solid dosage form is also more acceptable to the average patient, especially if there was a significantly reduced toxicity associated with the smaller dose required to produce freedom from tumors following surgical intervention.

What I claim is:

1. An oral pharmaceutical dosage form comprising:

a plurality of particles further comprising at least one therapeutic agent that is active against disorders of the mammalian colon, and at least one mucoadhesive; and

an enteric coating surrounding each particle.

2. The oral pharmaceutical dosage form of claim 1 wherein the enteric coating is an acrylic acid copolymer coating that swells in an aqueous enviornment having a pH of from about 6.8 to about 7.2 or higher.

3. The oral pharmaceutical dosage form of claim 1 wherein the mucoadhesive is at least one hydroxycellulose.

4. The oral pharmaceutical dosage form of claim 3 wherein the mucoadhesive is hydroxyproplymethylcellulose.

5. The oral pharmaceutical dosage form of claim 1 wherein the therapeutic agent is at least one antineoplastic compound.

6. The oral pharmaceutical dosage form of claim 5 wherein the antineoplastic compound is selected from the group alkylations agents such as alkylsulfonates, aziridines, epoxide, nitrogen mustards, nitrosureas, and antibiotics, and 5-fluorouracil.

7. The oral pharmaceutical dosage form of claim 6 wherein the antineoplastic compound is 5-fluorouracil.

8. An oral pharmaceutical dosage form comprising:

a plurality of particles further comprising from about 5 to about 50 wt% 5-fluorouracil, and from about 50 to about 95 wt% hydroxyproplymethylcellulose; and

from about 0.1 to about 10 wt% of a coating of at least one acrylic acid copolymer that swells in an aqueous environment having a pH of from about 6.8 to about

7.2 or greater.

9. The oral pharmaceutical dosage form of claim 8 wherein the plurality of particles are enclosed in a capsule.

10. The oral pharmaceutical dosage form of claim 8 wherein the plurality of particles are formed into a tablet.

11. The oral pharmaceutical dosage form of claim 8 wherein the plurality of particles are placed in a solution having a pH less than about 6.8.

12. A method for treating disorders of the mammalian colon wall comprising:

preparing an oral pharmaceutical dosage form including a plurality of particles further comprising at least one therapeutic agent that is active against disorders of the mammalian colon and at least one mucoadhesive, and a coating each particle with at least one acrylic acid copolymer that swells at a pH of from about 6.8 to about 7.2 or higher; and

administering the pharmaceutical dosage form orally to a mammal.

13. The method of claim 12 wherein the mammal is a human.

14. The method of claim 12 wherein the mucoadhesive is at least one hydroxycellulose compound.

15. The method of claim 14 wherein the mucoadhesive is hydroxyproplymethylcellulose.

16. The method of claim 12 wherein the therapeutic agent is at least one antineoplastic compound.

17. The method of claim 16 wherein the antineoplastic compound is selected from the group alkylsulfonates, aziridines, epoxide, nitrogen mustard, nitrosureas, and 5-fluorouracil.

18. The method of claim 6 wherein the antineoplastic compound is 5-fluorouracil.

19. The method of claim 12 wherein the disorder of the mammalian colon wall is colon cancer.

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(57) Abstract

This invention is an enteric-coated granular formulation capable of targeting or persisting in the colonic region and a method for using the formulation to treat disorders of the colon wall.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22352

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 077 956 A (TANABE SEIYAKU) 4 May 1983	1,2,5-7, 12,13, 16-19
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Y	see claims 1-3	8-11,14, 15

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